DETAILED ACTION

Claims 1-13, 15-18, 20-30, 34, 37-45 and 48-58 are pending in this application and were examined on their merits.

The objection to the Specification because the title was not descriptive has been withdrawn due to the Applicant's amendments to the title filed 10/28/09.

The objection to Claim 18 because of minor spelling informalities has been withdrawn due to the Applicant's amendments to the Claims filed 10/28/09.

The rejection of Claims 3, 7, 9, 15 and 18 under 35 U.S.C. § 112, 2nd paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention has been withdrawn due to the Applicant's amendments to the Claims filed 10/28/09.

The rejection of Claim 35 under 35 U.S.C. § 112, 2nd paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention has been withdrawn due to the Applicant's cancellation of the claim in the amendments to the Claims filed 10/28/09.

The rejection of Claim 41 under 35 U.S.C. § 112, 2nd paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention has been withdrawn due to the Applicant's amendments to the Claim filed 10/28/09.

The rejection of Claim 45 under 35 U.S.C. § 112, 2nd paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention has been withdrawn due to the Applicant's amendments to the Claim filed 10/28/09.

The rejection of pending Claims 1-7, 10-13, 16, 17, 20, 22-30, 40-45 and 48-51 under 35 U.S.C. §103(a) as being unpatentable over Tuompo *et al.* (US 5,714,343) has been withdrawn due to the Applicant's amendments to the Claims filed 10/28/09.

The rejection of pending Claims 1, 3, 4, 6, 7-11, 15, 17, 20-25, 27, 28, 34, 39 and 48-51 under 35 U.S.C. §103(a) as being unpatentable over Laine *et al.* (US 6,090,573) has been withdrawn due to the Applicant's amendments to the Claims filed 10/28/09.

Claim Objections

Claim 43 is newly objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Claim 43 contains the same limitations as parent Claim 41.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-13, 15-18, 20-30, 34, 37-45 and 48-58 are newly rejected under 35 U.S.C. §103(a) as being unpatentable over Tuompo *et al.* (US 5,714,343) in view of Koumara *et al.*(US 5,591,554).

Tuompo *et al.* teaches a method for the detection of viable microorganisms (bacteria), the method comprising a) passing a known volume of liquid medium through a filter from influent side to effluent side in a closed, sterile filter device (Fig. 1) thereby

concentrating and retaining microorganisms (bacteria) present on the filter device influent side, b) contacting the influent side of the filter with a liquid vehicle (test solution) containing a chromagenic enzyme substrate such as nitroblue tetrazolium (NBT) which forms a blue precipitate or soluble tetrazolium bromide (MTT) which forms a purple soluble stain; that through contact with constitutively expressed microbial dehydrogenase will produce a detectable moiety, and c) allowing the chromogenic substrate to interact with the microorganisms (bacteria) for a period of time wherein the interaction is not terminated and detecting the colored product retained on the filter and correlating the detection of the colored product to the presence of bacteria in the sample (Column 8, Claim 1 and Column 9, Claims 1, 2, 4, 5 and 7 and Column 4, Lines 66-67 and Column 5, Lines 1-25); and wherein the contaminating bacteria are subjected to a selective pH of 6.5, 7.2 or 8.5 prior to filtration (Column 4, Lines 66-67 and Column 5, Lines 1-16)

Tuompo *et al.* teaches wherein prior to step a) the medium is pre-filtered (Column 3, Lines 35-52), wherein the viscosity is reduced by means of dilution prior to step a) (Column 4, Lines 66-67) or treatment with a non-ionic detergent (Column 3, Lines 48-57), wherein the prior to step a) the medium is treated with a non-selective growth enhancer for microorganisms (1% glucose or fructose) in the medium (Column 5, Line 1), wherein the filter has a pore size from 0.75 to about 1.2 µm (Column 2, Lines 45-47), wherein several different known volumes of medium containing different amounts of bacteria were passed through a filter in step a) (Column 5, Table 1), wherein

detection is performed in a microtiter plate (Column 5, Lines 5-7), wherein the bacteria are subjected to a selective pH incubation (signal enhancing substance) prior to step a) (Column 5, Table 1) and wherein the water soluble substrate MTT, which is not retained on the fiber can be used for spectrophotometric methods of detection in the liquid vehicle (Column 3, Lines 22-23).

Tuompo *et al.* teaches that the method can be used on liquid samples from the wood and pulp industry, the sugar industry or urban waste water (Column 2, Lines 30-33).

It is inherent in the method of Tuompo *et al.* that the liquid vehicle containing the chromogenic substrates comprises multiple substrates providing signals that are combined into one measured signal value because the liquid vehicle contains multiple molecules of the chromogenic substrate MTT which combine to give a total, measurable color formation, and that the amount of substrate does not limit the rate of production of the detectable moiety.

It is inherent in the method of Tuompo *et al.* that the liquid medium used in the incubation prior to step a) would have a reduced viscosity due to the presence of detergent in the medium because this is a property of detergents, which lower the surface tension of liquids.

It is further inherent that the rate of production of the detectable moiety would be a linear function of the quantity of bacteria in the medium as it logically follows that more bacteria would equal more available enzyme for reaction with the substrate and result in a greater rate of production over a sample containing less bacteria (the velocity of an enzyme catalyzed reaction is first order in enzyme concentration). It is an inherent property of the filter device of Tuompo *et al.* would be disposable as nearly everything can be considered "disposable", giving the term its broadest, reasonable interpretation and only depends on the materials used.

The teachings of Tuompo *et al.* were discussed above.

Tuompo *et al.* did not teach a method wherein step d) requires the liquid vehicle is evacuated from the influent side of the filter by forcing the liquid vehicle through the effluent side of the filter and step e) performing a quantitative or qualitative detection of the detectable moiety in the evacuated liquid vehicle and correlating the detection of the moiety to the amount of presence of contaminants in the sample; wherein the liquid sample was environmental water, wherein the medium is an air sample; wherein the enzyme is alkaline phosphatase; wherein the closed, sterile filter device integrates the filter and filter housing into one irreversibly closed structural unit wherein longest cross-sectional axis of the closed, sterile filter device does not exceed a length of 10cm; wherein the detectable moiety is detectable in an amount of at most 100 picomoles, 50 picomoles, 20 picomoles, 10 picomoles or 1 picomole; wherein the substrate that produces a detectable moiety by being cleaved by an enzyme characteristic for the

contaminants is a methylumbelliferyl such as 4-methylumbelliferyl phosphate free acid; wherein the detection step is performed by measuring fluorescence of the detectable moiety and wherein fluorescence is measured directly on the liquid vehicle without interruption; or wherein the contaminants are filamentous fungi or yeast; or wherein the at least one substrate includes at least two substrates that produce detectable moieties providing distinguishable signals.

Koumura *et al.* teaches a method wherein a liquid sample of viable microorganisms (bacteria, fungi such as the yeast *Saccharomyces*, etc [Column 3, Lines 36-38].) are contacted with methylumbelliferyl derivatives, such as 4-methumbelliferyl phosphate (inherently the free acid and substrate for alkaline phosphatase) (Column 3, Lines 3-9), in a liquid vehicle that upon hydrolysis by enzymes characteristic to the microorganisms form fluorescent products which are measured directly in the liquid vehicle (Column 11, Claim 1).

It would have been obvious to one of ordinary skill in the art at the time of the invention to evacuate (elute) the colored enzymatic reaction product by applying either an elevated pressure on the influent side of the filter or applying a lowered pressure on the effluent side of the filter because one of ordinary skill in the art would have recognized this as an automation of the gravity filtration process taught by Tuompo *et al.* when using the MTT substrate and the automation of a previously manual activity is *prima facie* obvious (See MPEP, *In re Venner).*

It would have been obvious to one of ordinary skill in the art at the time of the instant invention to modify the method of Tuompo *et al.* for the detection of viable microorganisms (bacteria) in liquid samples to detect microorganisms in environmental water samples wherein the detectable moiety cleaved by enzymes characteristic for contaminating microorganisms is in picomolar amounts because Tuompo *et al.* teaches that the method is applicable to many varied liquid samples from biological fluids to industrial or waste water liquids as well as other liquid samples in which the presence of microorganisms is of interest and because it is desirable to detect contamination using the smallest amount of detectable moiety possible. One of ordinary skill in the art would have been motivated to make this modification because the reference clearly teaches its suitability in assaying a wide range of liquid samples. Further, one of ordinary skill in the art would have recognized the advantageous property of detecting a contaminating microbe in the least amount possible, as obviously detecting a small amount of contamination is better than only detecting gross contamination. One of ordinary skill in the art at the time of the invention would have recognized that the result-effective adjustment of conventional working parameters (e.g., determining the least amount of detectable substrate released by microbial action) is deemed merely a matter of judicious selection and routine optimization which is well within the purview of the skilled artisan.

While the reference does not teach the integration of the filter and filter housing into one irreversibly closed structural unit, wherein longest cross-sectional axis of the closed, sterile filter device does not exceed a length of 10 cm, those of ordinary skill in the art would have recognized that making the structure irreversibly closed and of a certain cross-sectional length are merely artisinal design modifications dependent upon personal preference and do not materially change the way the device functions. There would have been a reasonable expectation in making these modifications because the reference clearly teaches the applicability of the method to assaying any liquid water samples suspected of containing microorganisms and because personal design choices of the devices used in biological methods and detecting miniscule amounts of fluorescent compounds are well known to those of ordinary skill in the art.

It would have been obvious to one of ordinary skill in the art at the time of the instant invention that although Tuompo *et al.* is directed to the detection of microbes in liquid samples, the extension to the detection of airborne microbes would not be precluded from the method as long as the filter were sufficient to retain the microbes thereon. Whether the microbes are air or liquid borne, as long as they are retained on the filter they can be assayed using the method of the reference. Further, the origin of the air sample to be assayed does not materially change the way the method works. Any sample of air can be assayed from any origin as long as any microbes therein are capable of being retained on the filter.

It would have been obvious to one of ordinary skill in the art at the time of the invention to combine the chromogenic filtration method for the detection of viable microorganisms (bacteria) as taught by Tuompo *et al.* with the use of methylumbelliferyl derivative substrates and direct measurement method of Koumura *et al.* because the use of fluorescent vs. chromogenic substrates in the detection of microorganisms is well known in the art. Both references teach the detection of bacteria with substrates which are either chromogenic or fluorogenic and which upon interaction with characteristic enzymes form either a colored or fluorescent product. Therefore, one of ordinary skill in the art would conclude that either substrate would be suitable for detection of microorganisms. Further, a combination of the two methods would also provide a method wherein both chromogenic and fluorogenic substrates are used to determine two enzymes simultaneously. The MPEP states:

> The selection of a known material based on its suitability for its intended use supported a prima facie obviousness determination in *Sinclair & Carroll Co. v. Interchemical Corp.*, 325 U.S. 327, 65 USPQ 297 (1945)

Response to Arguments

Applicant's arguments, see Remarks, filed 10/28/09, with respect to the rejection(s) of claim(s) 1, 3, 4, 6, 7-11, 15, 17, 20-25, 28, 34, 39 and 48-51 under 35 U.S.C. § 103(a) in view of Laine *et al.* (US 6,090,573) have been fully considered and are persuasive. Therefore, the rejection has been withdrawn.

However, upon further consideration, a new ground(s) of rejection is made in view of Tuompo *et al.* in view of Koumura *et al.* above.

Applicant's arguments filed 10/28/09 have been fully considered but they are not persuasive.

The Applicant argues that Tuompo *et al.* teaches detection on a filter not in the liquid vehicle as recited in the instant Claim 1 and that the reference further fails to teach or suggest two subsequent steps wherein the first step is evacuation of liquid vehicle from the influent side of a filter and a second step of detection of detectable moiety in the evacuated vehicle (Remarks, Pg. 17, Lines 11-14 and Pg. 18, Lines 1-2).

This is not found to be persuasive for the following reasons, as discussed above, Tuompo *et al.* teaches the use of a soluble substrate which will flow through the filter after contacting the entrapped microorganisms and be detected in the liquid vehicle by spectrophotometry.

It would have been obvious to one of ordinary skill in the art at the time of the instant invention to automate the manual process of gravity evacuation of the liquid vehicle from the influent side to the effluent side of the filter as a means of increasing the amount of detectable moiety in the medium by reducing the amount of detectable

moiety retained on the filter similarly to wringing out a sponge vs. letting the sponge passively drip. As discussed above, the reference already teaches the step of detecting detectable moiety in the evacuated vehicle.

The Applicant asserts that as Tuompo *et al.* recommends the use of a detectable moiety which will remain on a filter surface (allegedly incompatible with the idea of evacuation of the detectable moiety) such that the method of the reference would have to be extensively modified to incorporate the evacuation and detection steps and that motivation to make these modification is not found in the reference, absent inappropriate hindsight (Remarks, Pg. 18, Lines 5-12).

This is not found to be persuasive for the following reasons, as discussed above, the reference suggests an embodiment wherein a soluble substrate is used to contact the filter entrapped microorganisms and then detectable moiety in the liquid vehicle is detected afterwards using spectrophotometry. It would not therefore, require "extensive modification" of the method of the reference as the evacuation step is inherently found in the gravity evacuation of liquid vehicle from the filter and detection of detectable moiety in the liquid sample is suggested by the reference. The MPEP states:

> "The use of patents as references is not limited to what the patentees describe as their own inventions or to the problems with which they are concerned. They are part of the literature of the art, relevant for all they contain." *In re Heck*, 699 F.2d 1331, 1332-33, 216 USPQ 1038, 1039 (Fed. Cir. 1983) (quoting *In re Lemelson*, 397 F.2d 1006, 1009, 158 USPQ 275, 277 (CCPA 1968))

In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971).

Conclusion

No Claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the

shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to PAUL C. MARTIN whose telephone number is (571)272-3348. The examiner can normally be reached on M-F 8am-4:30pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jon Weber can be reached on 571-272-0925. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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01/08/09

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